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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
KISHORE, GOLLAMUDI S

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 04/25/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/398,934	Ahl
Examiner	**Art Unit**
Gollamudi S. Kishore, Ph.D	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 26, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-53* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Filing under 1.114 dated 10-26-01 is acknowledged.

Claim Objections

1. **The amendment A dated 11-2-00 is improper as the amended claims, all of which are added claims, must have been underlined. These claims do not comply with rule 1.173.**

   a. **The amendment B dated 8-27-01 is improper for the same reasons as above. Amendment B has not been entered, since it does not comply with 37 CFR 1.175 (c).**

These amendment should be resubmitted.

Claim Rejections - 35 U.S.C. § 112

2. **The following is a quotation of the first paragraph of 35 U.S.C. 112:**

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

3. **Claims 1-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for drop in blood pressure as the adverse reactions and indomethacin as the drug which can treat this pressure drop, does not reasonably provide enablement for generic 'adverse reactions' and 'anti-inflammatory agent'. The specification does not enable any person skilled in the art**

to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

Instant invention is based on the observation that liposomes made with specific phospholipids cause a drop in blood pressure and that indomethacin is able to correct this blood pressure drop. Indomethacin might come under the classification of 'anti-inflammatory drugs' because it has anti-inflammatory properties; just because indomethacin also possesses blood pressure modulating properties, one cannot conclude that all anti-inflammatory agents which is a generic name and includes a variety of compounds are also blood pressure modulating agents. Applicants have provided no rationale for this concept. Secondly and most importantly, liposomes are known in the art as drug delivery agents for the past 20 years and as the prior art would indicate that even the administration of empty liposomes is known. Applicants have not shown that or provided adequate description as to what other adverse reactions are caused by the liposomes and presented a rationale for the capability of indomethacin to correct all the adverse reactions. Broad claims must have broad basis of support in the specification; in the absence of such support, claims must be limited to liposomes made with specific phospholipids and the drop in blood pressure as the adverse reaction and indomethacin as the compound which is able to correct this adverse reaction.

Applicant's arguments have been fully considered, but are not found to be persuasive.

Applicant argues that the specification as filed does indeed enable the full scope of the claims. Applicant argues that liposomes referred by the examiner are merely preferred and not required. These arguments are not found to be persuasive since as pointed out above, instant claims are drawn to a method of treatment of adverse reactions caused by liposomes by administering the same liposomes which cause the adverse reactions together with an anti-inflammatory agent. First of all, the term, liposomes is a generic term applied to bilayer structures formed by amphiphilic molecules which can be phospholipids or non-phospholipids. Applicant has not shown that the adverse reactions are because of the bilayer nature of the liposomes regardless of what they are made from. Secondly, applicant has not established the connection between generic 'anti-inflammatory agent' (which term includes structurally dissimilar compounds) and the ability of these structurally dissimilar compounds to be able to be effective against presumable adverse reactions such as lethargy, nausea, vomiting, defecation, diarrhea or other conditions (see applicant's response on page 7). For example, aspirin is a widely used anti-inflammatory agent in the world. The examiner is unaware of any publication to show that aspirin is effective against lethargy or nausea or defecation. As was also pointed out in the earlier actions, just because one chemical which incidentally comes under the category of 'anti-inflammatory agent' and able to counteract the drop in blood pressure caused by phospholipid liposomes, one cannot reasonably come to the conclusion that all chemicals which are classified based on their common function would counter the drop in blood pressure caused by liposomes. If

that were to be the rationale, one could come to the conclusion that just because aspirin prevents heart attacks, Advil, Tylenol and morphine or other similar compounds would also have an effect just as aspirin because they come under the category of 'pain killers'; or just because the heart drug, minoxidil is able to grow hair, other heart drugs would also grow hair. The examiner has provided sufficient scientific basis for his position and applicant has not provided convincing arguments to overcome this rejection. The rejection is maintained.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

5. Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, line 7, 'bilayer' lacks an antecedent basis. 'functional group' in claim 14 lacks an antecedent basis in claim 12.

In claim 16, the Markush group is improper; it contains overlapping terms.

Claim Rejections - 35 U.S.C. § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 25, 26, 27, 45, 47, 53 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 60152414 or JP 63264517.

Both JP references disclose liposomes containing indomethacin (note the abstracts) and a method of treatment. Instant claim language does not does not exclude liposomal indomethacin taught by the references.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that in instant invention, the anti-inflammatory agent is outside the liposomes and in the references, it is inside. This argument is not found to be persuasive since the instant claim language does not exclude the presence of anti-inflammatory agent inside the liposomes and there is no evidence in the prior art that the unencapsulated indomethacin has been removed. Therefore, the reference meets the requirements of instant claims.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 18, 25, 28, 45 and 53 are rejected under 35 U.S.C. 102(b) or 102 (e) as being anticipated by Meybeck (5,443,839).

Meybeck teaches liposomal compositions containing scutellaria extracts, various compounds in this extracts and a method of delivery of the active agent for the treatment of allergies (note the abstract, col. 2, line 26 through col. 5, line 64, Examples and claims).

Note: the 102(b) rejection is made since it would appear that there is no support for the claims in the originally filed application (this reissue application is a CIP of two prior applications). This rejection however, will be reconsidered.

9. Claims 18, 19, 21, 23, 24, 25, 27, 33-36, 43-45 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Young (5,023,087).

Young discloses a method of treating an animal with liposomes containing an anti-inflammatory agent (steroids) and empty liposomes; the liposomes are either unilamellar or multilamellar (note the abstract, col. 4, line 62 et seq., col. 10, line 35 et seq., examples). Young meets the limitations of instant composition claims since the steroid is not encapsulated in the same liposomes. That is, Young discloses empty liposomes and the steroid is not in the same liposomes. Since instant claims do not recite any specific bioactive agent, water present in the liposome cavity reads on instant claims since water is bioactive, meaning that it participates in biochemical reactions.

Applicant's arguments have been fully considered, but are not found to be persuasive. With regard to the composition claims (25, 27, 33-36, 43-45 and 53), applicants

argue that Young discloses empty liposomes and liposomes containing steroidal anti-inflammatory agent, but does not disclose liposomes containing active agent and steroid outside the liposomes. This argument is not found to be persuasive for the following reasons. First of all, the composition claim 25 does not recite any bioactive agent. Secondly, according to the claim language, the anti-inflammatory agent outside the THE liposome. Young teaches two populations of liposomes and one of the populations is the empty liposome population. That means, the anti-inflammatory agent in Young is not present in this population of liposomes and therefore, it is present OUTSIDE these liposomes. Previously the examiner argued that the water in Young could be construed as a bioactive agent and still holds the same position. Even assuming it is not a bioactive agent, Young's empty liposomes contain tocopherol (vitamin) and according to instant specification, vitamins are bioactive agents. Furthermore, the empty liposomes of Young contain phospholipids and it is well known in the art that phospholipids are used for atherosclerosis. The reference of Williams (1984) is cited of interest in this context. With regard to the method claims, applicants argue that even if the compositions disclosed by Young, new method of using such compositions would not necessarily be anticipated. This argument is not found to be persuasive since instant method claims recite either a method of delivering or method of treating and Young teaches both.

Applicant argues that Young is concerned with delivering a drug entrapped in liposomes rather than counter-acting the adverse reactions caused by liposomes. This argument is not found to be persuasive since Young uses the same liposome composition and an anti-inflammatory agent; in essence, Young discloses the same method of administration; therefore, any adverse reactions caused by liposomes and their reduction by the anti-inflammatory agent which is also administered is inherent in Young, whether they are recognized by Young or not. Applicant's arguments with regard to the composition claims have been noted, but are not found to be persuasive. Instant claims do not recite 'unencapsulated anti-inflammatory agent'. The claims require only that the anti-inflammatory agent be not in THE liposomes (see claim 25 for instance). Young teaches two populations of liposomes and the steroids are in one set of liposomes and the other liposomes are empty.

Claim Rejections - 35 U.S.C. § 103

10. **The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

11. **Claims 18-32, 34-35, 41-42, 45, 47, and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young cited above by itself or in combination with either JP references cited above or Meybeck.**

Young does not teach non-steroidal anti-inflammatory agents. However, it is deemed obvious to one of ordinary skill in the art to use any anti-inflammatory agent including indomethacin if the adverse reaction from the liposomal administration is inflammation; one would be motivated further to administer indomethacin since JP references teach the use of indomethacin and scutellaria extract respectively for such a purpose.

Applicants' arguments have been fully considered, but are not found to be persuasive. Applicants' arguments once again pertain to lack of anti-inflammatory agent outside the liposomes and that Young's liposomes are empty liposomes. These arguments have been addressed above.

12. Claims 33-44 and 48-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Young cited above, further in view of Park (BBA, 1992): or Park in view of Young.

What is lacking in Young is the teaching the modification of the surface of the liposomes using carboxylic acids.

Park teaches that liposomes modified with carboxylic acids prolong the circulation of the liposomes (note the abstract). Park's teachings are generic with respect to the active agent incorporated.

The modification of the surface of the liposomes of Young using carboxylic acids would have been obvious to one of ordinary skill in the art since such a modification results

in the liposomes having longer circulation. Alternately, to encapsulate an anti-inflammatory agent as the active agent in the liposomes of Park would have been obvious to one of ordinary skill in the art since liposomes are known drug delivery agents and the reference of Young shows the knowledge in the art of encapsulation of anti-inflammatory agents in liposomes for delivery.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Young's empty liposomes have been addressed above.

Applicant argues that Park fails to teach or suggest a liposome composition comprising a liposome encapsulated bioactive agent, an anti-inflammatory agent which is not encapsulated. These arguments are not persuasive since Park is suggestive of a motivation to modify the surface of the liposomes by inclusion of carboxylic acids; the examiner points out that applicants themselves in their previous response acknowledged that it may be correct to modify the teachings of Young in view of Park to include carboxylic acids in the liposome structure.

13. **Claims 29-32 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 63264517 or Young cited above, by themselves, in further in view of Park (BBA, 1992): or Park in view of either of Young or JP as set forth above, and in further combination with Cheng (Investigative Radiology, vol. 22, 1987).**

The references of JP, Young and Park do not teach the inclusion of a contrast agent in the liposomes. Such an inclusion however, would have been obvious to one of ordinary skill in the art if the purpose is to locate the treatment site as well as treat it since the reference of Cheng shows the awareness in the art of encapsulating contrast agents in liposomes (note the abstract).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Cheng does not teach the use of the contrast agent in conjunction with the anti-inflammatory agent. This argument is not found to be persuasive since the reference of Cheng shows the use of liposomes for imaging purposes and it is within the skill of the art of medicine to image the tissue which needs to be treated and treat it at the same time.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *G.S. Kishore* whose telephone number is (703) 308-2440.

The examiner can normally be reached on Monday-Thursday from 6:30 A.M. to 4:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T.K. Page, can be reached on (703)308-2927. The fax phone number for this Group is (703)305-3592.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [thurman.page@uspto.gov].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-1235.

Gollamudi S. Kishore, Ph. D

Primary Examiner

Group 1600

gsk

April 19, 2002